EDITORIALS

Physical Activity and Breast Cancer: Is There a Link?

*Joanne F. Dorgan**

Physical activity has diverse physiologic effects through which it could potentially alter breast cancer risk. Currently, the most prominent hypothesis is that physical activity may lower risk through hormonal mechanisms. Estrogens are mitogenic to breast epithelial cells and are believed to play a key role in breast cancer promotion and possibly initiation *(1)*. Older age at menarche, younger age at menopause, and perhaps a higher frequency of long and irregular menstrual cycles lower breast cancer risk *(2)*. Compared with their more sedentary peers, highly trained athletes and dancers *(3)*, and possibly recreational athletes *(4,5)*, have delayed menarche and an increased frequency of long or irregular menstrual cycles. Although obesity is inversely related to the risk of premenopausal breast cancer, after menopause occurs, estrogens are synthesized from androgens in adipose tissue and obesity is directly related to risk *(6)*. Physically active women of all ages are leaner than their more sedentary counterparts *(7)*, but leanness is a major determinant of serum estrogen concentrations only for postmenopausal women *(8)*. Because of its biological plausibility and consistency, the hypothesis that physical activity lowers breast cancer risk through hormonal mechanisms is intuitively appealing.

In this issue of the Journal, Rockhill et al. *(9)* present findings from the Nurses' Health Study II on the relationship between nonoccupational physical activity and breast cancer risk in women up to 48 years of age at diagnosis. The analysis was based on 104 468 female nurses followed for 6 years, during which time 372 invasive breast cancers were diagnosed. Nurses who frequently participated in strenuous activities during late adolescence had essentially the same risk of developing breast cancer as those nurses who never participated in such activities (relative risk [RR] = 1.1; 95% confidence interval [CI] = 0.8–1.6). Similarly, nurses who spent the most time engaged in moderate and strenuous nonoccupational activities at 25–42 years of age had the same risk of breast cancer as those who spent the least time in these activities (RR = 1.1; 95% CI = 0.8–1.5). Results were unchanged when adjusted for potential confounders or stratified on possible effect modifiers.

The lack of even a suggestion of a protective effect of nonoccupational physical activity for breast cancer in young women from the Nurses' Health Study II is disappointing, but not surprising. Although Bernstein et al. *(10)* reported a significant 60% lower risk of breast cancer at a young age for women who regularly participated in recreational activities, a recent study by Gammon et al. *(11)* did not detect an association. Conflicting results also emerge from studies [reviewed in *(12)*] of postmenopausal women and of occupational activity. Inverse associations of physical activity with breast cancer are reported more often than null or positive associations, but frequently risk estimates are small and statistically nonsignificant, a dose–response relationship is not seen, or the association is limited to a subgroup of participants.

Physical activity is one of numerous determinants of age at menarche and menstrual function, and other factors may be more important for most women. Associations of recreational sports activity with age at the onset of menses are inconsistent *(4,13)*. In addition, in a study of college women *(14)*, moderate physical activity had only a minimal association with cycle length, as estimated from menstrual diaries. Physical activity contributes to energy balance, but other factors including genetics also affect body weight *(7)*. Age at menarche and, for postmenopausal women, obesity are established but not particularly strong risk factors for breast cancer; the association with menstrual cycle characteristics is less well established *(2)*. Participants in the Nurses' Health Study II *(15)* who were older at menarche had a 34% reduction in the risk of premenopausal breast cancer. Those who had longer or irregular cycles had a 20%–60% reduction in risk. This cohort is still young, and few members are postmenopausal. In another large cohort *(16)*, the most obese postmenopausal women had a 50% elevation in the risk of breast cancer. Therefore, even if physical activity prevents breast cancer by contributing to a delay or disruption in menstrual function in young women and the maintenance of ideal body weight in older women, within the range typical of women in the United States, the effect of physical activity on risk, if one exists, is likely to be modest.

Assessment of physical activity in epidemiologic studies is extremely difficult. Typically, questionnaires with varying degrees of specificity are used. Although most are not validated, the questionnaire used in the Nurses' Health Study II was evaluated against multiple, 7-day activity diaries *(17)*. The correlation between the two instruments' measures of physical activity was .62, which compares favorably with other activity questionnaires *(18,19)*. Findings on reproducibility were similar. Although questionnaires may yield reasonably valid and reliable estimates of physical activity, they misclassify some individuals, which will attenuate and could obscure weak associations of physical activity with breast cancer. Age at onset of menses and frequencies of menstrual disturbances in elite and possibly in recreational athletes differ by sport, intensity and duration of exer-

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cise, prior conditioning, and, for menstrual disorders, by gynecologic age *(20)*. Ascertainment of more detailed information on these characteristics may increase the likelihood of detecting associations with breast cancer.

If physical activity lowers breast cancer risk, it seems that total physical activity would be protective. However, most studies evaluate the association of either recreational or occupational activity with risk. The Nurses' Health Study II assessed the relationship of breast cancer with nonoccupational (recreational plus aerobic household) physical activity. Although the Nurses' Health Study II cohort includes only nurses, some may have stopped working. For those who continued to work, occupational physical activity could differ substantially, depending on the amount of time spent in patient care. Potential for confounding by physical activity at work was not considered in an otherwise very thorough analysis of nonoccupational physical activity, possibly because of a lack of necessary data. Because physical activity behaviors change and individuals' levels of activity at different ages are not highly correlated, physical activity assessed at a single point in time may not reflect longer term patterns *(21)*. In the Nurses' Health Study II, physical activity was assessed for two limited-time intervals. The strong inverse association of physical activity with breast cancer in the study by Bernstein et al. *(10)* was based on regular participation in physical activities throughout the reproductive years, suggesting that measurement of physical activity over the relevant time interval may be necessary.

The Nurses' Health Study II is one of the largest cohorts of women, but even larger studies may be needed for sufficient power to test fairly the association of physical activity with breast cancer. More extensive studies of subgroups known to include highly physically active women, similar to the study of college athletes by Frisch et al. *(22)* when they first reported the inverse relationship of physical activity to breast cancer, might also prove to be informative.

Physical activity has diverse physiologic effects. The relationship of physical activity and breast cancer probably is complex and mediated through multiple metabolic processes. Some processes, like stimulation of immune function *(23)*, could decrease risk, whereas others, like increased oxidative stress *(24)*, could increase risk. The balance could result in a stronger or a weaker association than suggested solely by the hormonal mechanisms described. The potential impact of modifying an attribute or behavior on disease incidence in a population depends not only on the strength of its association, but also on the proportion of the population who exhibit the characteristic. Approximately one third of women in the United States who are older than 50 years are overweight *(25)*. Therefore, even if physical activity only reduced the risk of breast cancer modestly through the proposed mechanisms, its impact on the incidence of breast cancer in the population could be substantial.

Physical activity is one of the few potentially modifiable breast cancer risk factors. Further research on its relationship to breast cancer is clearly indicated. Given the current evidence, recommendations to premenopausal women to increase their physical activity with the specific aim of preventing breast cancer would be premature. However, recommendations to postmenopausal women to increase physical activity as part of a program to achieve or maintain ideal body weight and consequently lower their risk of breast cancer seem reasonable. Furthermore, all women can be encouraged to increase their physical activity to prevent cardiovascular disease, osteoporosis, diabetes, and possibly colon cancer, as well as to improve their sense of well-being.

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Gene Therapy for Lung Cancer—an Application for Cationic Lipid-Mediated Gene Delivery?

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In the United States, smoking-induced lung cancer is the leading cause of cancer death in both men and women. While the incidence of lung cancer in men appears to have reached a plateau and has begun to decline, the incidence in women continues to increase and at present is approximately 42 cases per 100 000 annually *(1).* Adenocarcinoma, squamous cell carcinoma, and large-cell carcinoma, which together make up the majority of lung cancers, collectively are termed ''non-small-cell lung cancers'' (NSCLCs). Patients with early stage NSCLC generally are treated with surgery, resulting in 5-year survival rates that range from 25% to 80%, depending on the stage of the disease *(1).* Several recent studies [reviewed in *(2)*] have shown that patients with inoperable, early stage NSCLC also can be treated effectively with radiation. Fewer alternatives are available for late stage disease; routine use of chemotherapy for late stage NSCLC is controversial.

Small-cell lung cancers (SCLCs), which make up approximately 20% of the total, generally are highly metastatic. In the roughly one third of patients who present with disease limited to the thorax, surgical resection is an option for localized tumors in highly selected cases, while chemotherapy or chemotherapy plus radiation therapy is an option for more disseminated thoracic disease *(1).* The median survival for patients with extensive disease, which occurs in two thirds of SCLC patients, is several months, even with chemotherapy *(1).* Overall, the 5-year survival rate for patients with lung cancer is 13% *(1).* Clearly, more effective alternative therapies are needed, and gene therapy is among the therapeutic modalities currently being considered.

Lung cancer appears to be the ultimate result of an accumulation of mutations in a stem cell with the potential to differentiate along multiple pathways *(1).* Multiple histologic states have been recognized, and the morphologic changes appear to be associated with progression of the disease. For example, the development of squamous cell lung cancer appears to progress from squamous metaplasia to dysplasia, carcinoma *in situ,* and finally invasive cancer *(3).* Although this stepwise histologic progression may reflect a progressive accumulation of mutations, evidence *(4)* also points to the possibility that similar mutations may reside in histologically normal bronchial epithelial tissue from smokers. As in some other forms of cancer, the mutational events leading to invasive lung cancer are not random. For example, mutations involving chromosomal regions 3p14 and 9p21 appear to be early events, while those involving the tumor suppressors Rb and p53, namely, chromosomal regions 13q14 and 17p13, respectively, appear to be later events *(4).*

Most mutations in the tumor suppressor gene p53 appear to precede the invasive phenotype of lung cancer *(3).* Given the roles of normal p53 in maintaining normal cell cycling and apoptotic responses *(5,6),* mutations in p53 may be important events that allow the premalignant tumor cell to become invasive. As a marker of the invasive phenotype, p53 has been proposed as an intermediate biomarker *(3).* Given the importance of mutations in p53 in the invasive phenotype, together with the fact that the majority of lung cancers are characterized by mutations in p53 *(7),* one could consider a therapeutic strategy based on countering the effects of these mutations. Such strategies are made more reasonable because of the trans-dominant effects of wild-type p53 in modulating the tumorigenic state and the apparent lack of toxicity when wild-type p53 is overexpressed in normal cells [*(8)* and references therein; *(9)*].

Clinical gene therapy trials with viral vectors containing p53 have already provided a conceptual framework for the treatment of localized tumors. Direct injection of an adenoviral vector bearing p53 into squamous cell carcinomas of the head and neck have shown antitumor activity *(10),* while p53-containing retroviruses have shown promise following direct injection into malignant lung lesions *(11).* Potential mechanisms by which p53 may mediate antitumor effects include direct effects on the transduced tumor cells, e.g., apoptosis or the induction of dormancy, and indirect effects on neighboring, nontransduced tumor cells, i.e., ''bystander'' effects *(12).* As an alternative to viral delivery systems, Zou et al. *(13)* reporting in this issue of the Journal are considering the use of cationic lipids. Although at a disadvantage in terms of potency when compared to viral vectors, cationic lipids may present advantages in the context of long-term administrations to multiple tumor sites dispersed over the bronchial epithelium. Cationic lipid vectors appear to be devoid of the specific immune responses that have been shown to accompany the administration of viral vectors in the lung *(14,15).* Indeed, a recent clinical trial in the cystic fibrosis arena *(16,17)* has demonstrated limited efficacy with the use of a highly concentrated, aerosolized formulation of cationic lipid.

It is important to point out, however, that the absence of specific immune responses to cationic lipid-based delivery systems does not necessarily imply that they are without considerable toxicity. For example, preclinical studies *(18,19)* have shown that the instillation of cationic lipid vectors into the mammalian lung results in dose-dependent acute toxicity characterized by cellular influxes and the production of cytokines. A recent clinical study *(17)* using a single aerosol administration of cationic lipid–plasmid DNA (pDNA) complexes also noted mild, acute flu-like symptoms. Some of these acute preclinical and clinical effects may be related to the recently recognized

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inflammatory properties of bacterial pDNA presented in the context of a cationic lipid *(20).* Although such effects may be reduced when cationic lipid–pDNA complexes are given as an aerosol, it will be important to minimize this potential toxicity. In addition to the acute effects of cationic lipids, little is known at present about the potential chronic toxic effects of these unnatural lipids in the lung. The ultimate metabolic fate of cationic lipids and the long-term effects of the parent lipid and its metabolites on the physiologic function of the lung are largely unknown. Obviously, it will be necessary to understand these effects before cationic lipid vectors can be used in a chronic disease setting.

A clinical investigation is planned to follow up on the promising initial preclinical results reported by Zou et al. *(13)* in this issue of the Journal. Clinical end points in viral trials in which malignant lesions have been treated have included direct measures such as tumor regression and verification of gene transfer and expression *(10,11).* Clinical end points for trials in which premalignant lesions are to be the targets may be more problematic. While it may be possible to document vector-specific gene transfer and expression of a transgene such as p53, not all premalignant lesions in an individual necessarily have both p53 alleles mutated; these lesions presumably would be unresponsive to the tumor-suppressive effects of such gene therapeutics. Assuming a best-case scenario, i.e., that a lipid-based gene therapeutic protocol with p53 or other gene (possibly in synergy with chemotherapy or radiation therapy) results in demonstrable effects on invasive lesions, how far in the direction of prophylaxis might such a gene therapeutic approach go? Would premalignant lesions become realistic targets for gene therapy, say with the use of an aerosolized cationic lipid-based vector? To be in this situation would imply that gene therapeutics had truly come of age as ''drugs.'' Currently, there are no gene therapeutics on the market. Ultimately, the results of future clinical trials using gene therapeutics will answer such questions.

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